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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,486	03/26/2004	Mitsuru Furusawa	690116.401C1	8553

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,486	FURUSAWA, MITSURU	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10,12-19,22-46,48,50-55,57-64,66-89 and 95-125* is/are pending in the application.

4a) Of the above claim(s) *3,5,32,39,40,48,50,77,84,85 and 95-125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 66-76, 78-83, and 86-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/684,141.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 2/26/2007 is acknowledged. After entry of the amendment, claims 1, 3, 5-10, 12-19, 22-46, 48, 50-55, 57-64, 66-89 and 95-125 are pending. Claims 3, 5, 32, 39, 40, 48, 50, 77, 84, 85 and 95-124 remain withdrawn as directed to non-elected inventions, and claim 125 is withdrawn as directed to a non-elected invention for reasons set forth below. Claims 1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 66-76, 78-83, 86-89 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action. Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn.

Election/Restrictions

Newly submitted claim 125 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 125 recites a method for regulating a conversion rate of a hereditary trait of a yeast cell by regulating the proofreading function of DNA polymerase of the yeast by site-directed mutagenesis, then subjecting the yeast to acclimation culture by increasing culture temperature. These are method steps not found in the elected invention of Group I, and thus represent a distinct invention from Group I.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 125 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

Claims 1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 66-76, 78-83, and 86-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high temperature resistance" in claim 1, line 7 and in claim 45, line 7 is a relative term which renders the claims indefinite. The term " high temperature resistance " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The temperature, i.e. as in degrees Centigrade, that the cells must be resistant to in order to infringe the claims cannot be determined, hence the metes and bounds of the claimed subject matter are unclear. This rejection affects all dependent claims. **This is a new rejection necessitated by amendment of the claims.**

Claim 1 recites the limitation "conversion of the yeast cell" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim. This rejection affects all dependent claims. **This is a new rejection necessitated by amendment of the claims.**

Claim 45 recites the limitation " the yeast cell" in line 7. There is insufficient antecedent basis for this limitation in the claim. This rejection affects all dependent claims. **This is a new rejection necessitated by amendment of the claims.**

Claims 1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 67-76, 78-83, and 86-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

methods using yeast DNA polymerase δ with a higher error-prone frequency than wild-type DNA polymerase δ and wherein the polymerase provides mismatched bases at a frequency of 10^{-6} or greater, does not reasonably provide enablement for methods using yeast DNA polymerase δ with a lower error-prone frequency than wild-type DNA polymerase δ, methods using prokaryotic DNA polymerase δ, or methods using polymerases with an error frequency less than 10^{-6}. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons made of record in the Office Action dated 8/25/2006, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) one of skill in the art would know how to make, use and modify a prokaryotic DNA polymerase δ; 2) the level of experimentation required to practice the claimed invention is not undue, and a comparison of the instant invention to the facts at issue in *Wands* indicates undue experimentation is not required, i.e. the production of monoclonal antibodies was not considered undue experimentation in the case of *Wands*, therefore neither should the production of the instantly recited DNA polymerase mutants with the claimed properties be considered undue experimentation; 3) relevant techniques are known in the art, and disclosed in the specification, that would allow the skilled artisan to generate mutants and screen them, e.g. as disclosed in Kokoska et al (of record).

Regarding 1), applicants assertions are not in dispute. However, there is no showing in the specification or the prior art of record of using any prokaryotic DNA polymerase in a

eukaryotic (e.g. yeast) cell in a functional manner. How, for example, would a prokaryotic DNA polymerase, after translation in the cytoplasm, find its way into the nucleus of a eukaryotic cell where gene replication takes place? Furthermore, merely changing residues in a known active site is the definition of unpredictability, as the skilled artisan cannot predict if they have created a functional DNA polymerase by mutating an active site, let alone created one with the claimed error frequency properties. Mutating the residues suggested by applicants may or may not create a functional DNA polymerase, and may or may not create an enzyme with the claimed properties (although creation of DNA polymerases with the claimed properties appears unlikely, see below). To determine this, the skilled artisan would have to discover for themselves that which applicants have failed to disclose: that is, which mutants, if any, might have the claimed properties by making and testing them, case-by-painstaking-case, in order to discover which might have the claimed properties.

Regarding 2) and 3), the instant claims do not recite producing and screening monoclonal antibodies, a predictable and well established art at the time of *Wands*. For example, monoclonal antibodies and their structure were well known at the time of *Wands*, and how to produce an antibody to literally any given protein antigen was also known. This is in contrast to the instant invention, wherein the claimed DNA polymerase mutants exhibiting error-prone frequencies of greater than 10^{-6} or less than wild-type were not known, nor was it entirely clear such DNA polymerases could be made. This is because in practicing the "relevant techniques" relied upon above by applicants, Morrison et al and Kokoska et al (both made of record in the previous Office Action) failed to produce a DNA polymerase with an error frequency greater than 10^{-6} (i.e. less fidelity) or greater than wild type (i.e. higher fidelity), let alone any high temperature

resistance mutants, as required by the instant claims. Furthermore, it seems that DNA polymerase mutations with high error frequencies are not viable (Morrison et al, 1994, cited by applicants, see the abstract), explaining why no DNA polymerase mutants with an error frequency greater than 10^{-6} were generated in the experiments of Morrison et al and Kokoska et al: cells bearing the mutations did not survive.

It is not disputed that one skilled in the art could generate numerous mutants of any given DNA polymerase, however, to generate a DNA polymerase with the claimed error-prone frequencies is not a well established technique, is not known in the art, and therefore it is considered unpredictable, and to require undue experimentation in order to produce the claimed DNA polymerases (if they indeed could be made).

Claim Rejections - 35 USC § 102

Claims 1, 6-10, 12-14, 16, 17, 23-25, 28-31, 33-38, 41, 42, 45, 46, 51-55, 57-59, 61, 66-70, 73-76, 78-83, 86, and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Morrison et al (EMBO J., 1993, cited by applicants). **This rejection is maintained for reasons made of record in the Office Action dated 8/25/2006, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Morrsion et al merely create a *pol3-01* mutant and examine the relationship between *pol3-01* and *pms*; and, 2) Morrison et al do not teach that "conversion" of a yeast cell confers high temperature resistance to the cell.

Regarding 1) it is unclear how this assertion mitigates against the instant rejection. For reasons of record, *POL3* is a DNA polymerase and thus the *pol3-01* mutant teaches certain limitations of the claimed subject matter. Regarding 2), the instant methods do not recite a positive process step wherein any "converted" yeast cells are selected for heat resistance. All that is required is that a "conversion" of the yeast cell occur. With regards to this limitation, it is noted that "conversion" as presently used means "mutation" or "evolution", see in particular ¶ [0279] of the published application, US 20050054597 A1. Thus, it is considered randomly mutating the genome of a yeast cell is "converting" it, as this is what occurs in the methods of the instant invention, and in the prior art, due to the lower fidelity of the mutated DNA polymerase(s) that replicates the yeast genome. There is no requirement in the instant claims that an actual high temperature-resistant yeast cell be prepared, or even selected from the pool of "converted" yeast. For reasons of record, Morrison et al teach "conversion" of yeast cells, i.e. induced random mutations throughout the yeast genome, followed by selection for URA3 or his7-2 reversion. Absent evidence to the contrary, some of the "converted" yeast cells would be heat resistant because of mutations in genes conferring heat resistance, although these heat resistant cells were not selected for in the teachings of Morrison et al. However, as discussed above, this selection is not a method step or a limitation of the instant claims.

Claims 1, 6, 9, 10, 12-14, 16, 17, 22-25, 28-31, 33-38, 41-46, 49, 51, 54, 55, 57-59, 61, 62, 73-76, 78-83, and 86-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Kokoska

et al (Mol. Cell. Biol., 2000). **This rejection is maintained for reasons made of record in the Office Action dated 8/25/2006, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Kokoska et al merely teach random mutagenesis of the POL3 gene; and, 2) Kokoska et al do not teach the limitations of the claimed invention.

Regarding 1), it is unclear how this assertion mitigates against the instant rejection. For reasons of record, *POL3* is a DNA polymerase and thus the *POL3* mutants of Kokoska et al teach certain limitations of the claimed subject matter. Regarding 2), these are merely vague, general assertions that Kokoska et al do not teach the claimed invention, with no attempt to point out how the instant claims define over the teachings of Kokoska et al. This is in contrast to the previous Office Action, wherein each limitation of the claims was addressed by pointing out, by page and paragraph, the locations within the Kokoska et al reference teaching the claim limitations. Thus, applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

The only limitation of the instant claims not previously addressed is that "conversion" of a yeast cell confers high temperature resistance to the cell. The instant methods do not recite a positive process step wherein any "converted" yeast cells are selected for heat resistance. All that is required is that a "conversion" of the yeast cell occur. With regards to this limitation, it is noted that "conversion" as presently used means "mutation" or "evolution", see in particular ¶ [0279] of the published application, US 20050054597 A1. Thus, it is considered randomly

mutating the genome of a yeast cell is "converting" it, as this is what occurs in the methods of the instant invention, and in the prior art, due to the lower fidelity of the mutated DNA polymerase(s) that replicates the yeast genome. There is no requirement in the instant claims that an actual high temperature-resistant yeast cell be prepared, or even selected from the pool of "converted" yeast. For reasons of record, Kokoska et al teach "conversion" of yeast cells, i.e. induced random mutations throughout the yeast genome, followed by selection for canavanine resistance or MMS sensitivity. Absent evidence to the contrary, some of the "converted" yeast cells would be heat resistant because of mutations in genes conferring heat resistance, although these heat resistant cells were not selected for in the teachings of Kokoska et al. However, as discussed above, this selection is not a method step or a limitation of the instant claims.

Double Patenting

Claims 1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 66-76, 78-83, and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 4, 6-47, 49, 51-76, 78-83, and 86-89 of copending Application No. 10/550,924. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '924 application recite all the limitations of the instant claims, nearly verbatim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. **This is a new rejection.**

The newly presented grounds of rejection based on obviousness-type double-patenting will not preclude the finality of this Action. This ground of rejection involves conflicting claims

in a copending application newly discovered by the Examiner (i.e. the application was not published until 4/5/2007, after the date of the first Office Action, 8/25/2006), which has the same inventor as the instant application. Applicants did not call the attention of the Office to this application until the IDS submitted 2/26/2007, again, after the first Office Action. Applicants will not be permitted to extend prosecution of the present application by reason of their inaction with regard to providing notice to the Office of conflicting claims in a copending application, the discovery of which necessitated the new grounds of rejection at this advanced state of prosecution. Indeed, with appropriate notice, these grounds of rejection clearly could have been incorporated in the prior Office Action. These circumstances are analogous to the policy of making an action final where Applicant's material amendments to the claims necessitate a new ground of rejection, since in both instances it is the applicant who caused the rejection to be applied after the case had received an action on the merits. See M.P.E.P. § 706.07(a).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER